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Cytokine polymorphisms in the Th1/Th2 pathway and susceptibility to non-Hodgkin lymphoma

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Abstract (196)

Studies have demonstrated that common polymorphisms in Th1 and Th2 cytokine genes can alter gene expression, modulate the balance between Th1/Th2 responsiveness, and influence susceptibility for auto-immune disorders, infectious diseases, and cancer. We analyzed one or more single nucleotide polymorphisms (SNPs) in 20 candidate Th1/Th2 genes in a population-based case-control study of non-Hodgkin lymphoma (NHL) (n = 518 cases, 597 controls) among women in Connecticut. SNPs in critical genes, *IL4*, *IL5*, *IL6,* and *IL10,* were associated with risk for NHL and in some instances with a specific histologic subtype. Analysis of four SNPs in the *IL10* promoter (-3575T>A, -1082A>G, -819C>T, and -592C>A) revealed that both the AGCC haplotype (OR = 1.54, 95% CI = 1.21-1.96, $P < 0.001$) and the TATA haplotype (OR = 1.37, 95% CI = 1.05-1.79, $P = 0.02$) were associated with increased risk for B cell lymphomas. In contrast, the *IL4* -1098G allele was associated with increased risk of T cell lymphomas (OR = 3.84; 95% CI = 1.79-8.22; $P < 0.001$). Further, the *IL10* and *IL4* SNP associations remained significant after adjusting for multiple comparisons. These results suggest that SNPs in Th2 cytokine genes may be associated with risk of NHL.

Introduction

Cytokines play a crucial role in the regulation of key pathways of immunity, the balance between cell mediated (Th1) and humoral (Th2) responsiveness. Th1 cells drive cellular immunity to fight intracellular pathogens including viruses and remove cancerous cells, whereas Th-2 cells control humoral immunity by up-regulating antibody production to protect against extra-cellular pathogens.[1,2] Select cytokines regulate the subpopulation of T-cell lymphocytes responsible for this balance. T helper 1 (Th1) lymphocyte cells produce IL-2 and interferon-gamma and promote cell-mediated immune responses. T helper 2 (Th2) lymphocyte cells produce IL-4, IL-5, IL-6, IL-10, and IL-13, which favor B-cell activation and immunoglobulin production. These cytokines can modulate lymphoid development, immune function.[3-10] Since immune dysfunction is thought to be at the underlying basis of lymphomagenesis, an imbalance in the regulation and expression of Th1 and Th2 cytokines, which are the fundamental messengers of adaptive immunity, could play an important role in the etiology on non-Hodgkin lymphoma (NHL) and its major subtypes. [11,12]

Genetic variation is common across the human genome. It is estimated that there are more than 7 million SNPs with a minor allele frequency of 5 to 10%. Though most SNPs are not functionally important, there is a subset of variants that alter the expression or function of a gene product.[13] These functional variants may alter disease risk, affect the observed phenotype, contribute to the pathogenesis of the disease, or alter the response to treatment.[3,6,10,14-19] Common genetic variants in candidate genes, or for that matter, pathways of genes, can be applied to genetic association studies in search of

genetic risk factors for disease susceptibility. Since the expression of Th1 and Th2 cytokines can be altered by germ-line genetic variants,[5] we studied the association between common polymorphisms in Th1 and Th2 cytokine genes and the risk of NHL.

Here, we report on the results of 39 SNPs drawn from 20 distinct Th1 and Th2 genes in a population-based case-control study among women in Connecticut. The SNPs analyzed in this study were chosen on the basis of prior functional data[15-18,20-28] and previous association studies or to help characterize the haplotype structure of the gene of interest.

Materials and methods

Study population. The study population has previously been described.[29-31] Briefly, between 1996 and 2000, all histologically-confirmed, incident cases of NHL (ICD-O, M-9590-9642, 9690-9701, 9740-9750) from Connecticut, New Haven were identified through the Yale Cancer Center's Rapid Case Ascertainment Shared Resource (RCA). Enrollment criteria included age 21-84 years, residence in Connecticut, female, alive at the time of interview, and without a previous diagnosis of cancer except for non-melanoma skin cancer. Of 832 eligible cases, 601 (72%) completed in-person interviews. Pathology slides (or tissue blocks) from all patients were obtained from the original pathology departments and specimens were classified using the Revised European-American Lymphoma (REAL) system by central review.

Female population-based controls from Connecticut were recruited by: 1) random digit dialing methods for those less than 65 years of age; or 2) random selection from

Health Care Financing Administration files for those aged 65 years or older. The participation rate was 69% for those contacted by random digit dialing and 47% for those contacted through health care records. Cases and controls were frequency matched on age (±5 years) by adjusting the number of controls randomly selected in each age stratum once every several months during the period of recruitment.

Data collection. The study was approved by Institutional Review Boards at Yale University, the Connecticut Department of Public Health, and the National Cancer Institute. Participation was voluntary, and written informed consent was obtained from all participants. Those who signed consent were interviewed by trained study nurses either at the subject's home or at a convenient location. Subjects were administered a questionnaire requesting information on demographic characteristics, family history of cancer, past medical condition and medication use, diet, occupation, smoking, and drinking.

Following the interview, subjects provided a 10 ml peripheral blood sample. Subjects for whom the blood draw was contraindicated, or who refused to participate in the blood-draw, were offered the option to provide buccal-cell cotton swab samples instead. In total, 76.7% (461/601) of interviewed cases and 74.6% (535/717) of interviewed controls provided a blood samples, and 11.0% (57) of cases and 10.4% (62) of controls provided buccal cell samples.

Genotyping and quality control. Genotyping was performed at the National Cancer Institute Core Genotyping Facility (http://cgf.nci.nih.gov). All TaqMan® assays (Applied

Biosystems Inc., Foster City, CA) for this study were optimized on the ABI 7900HT detection system with 100% concordance with sequence analysis of 102 individuals as listed on the SNP500Cancer website (http://snp500cancer.nci.nih.gov).[32] We selected 39 SNPs in 20 Th1/Th2 immune genes based on the following criteria: minor allele frequencies greater than 5%, laboratory evidence of function, or prior association with human disease studies (Table 1). Due to a limited amount of DNA available for subjects who provided only buccal cells, we first genotyped subjects who provided a blood sample. If there was suggestive evidence, or if we had a relatively high prior that a given SNP was associated with risk of NHL, genotype analysis proceeded to include subjects who provided buccal cell samples. Among the 39 SNPs, 15 were genotyped only in subjects who provided a blood sample (Table 1). We observed a random drop-out for amplification and for samples that amplified yet could not be determined due to ambiguous results. In addition, the total number of cases and controls for which genotyping data were available varied because there was a limited amount of DNA available. Data on 8 of the 39 SNPs for Caucasian study subjects (noted in Table 1) were contributed to a pooling effort by the InterLymph case-control consortium of lymphoma studies.[33]

Duplicate samples from 100 study subjects and 40 replicate samples from each of two blood donors were interspersed throughout the plates used for genotype analysis. The concordance rates for QC samples were between 99% and 100% for all assays. The genotype frequencies for four SNPs [*IFNGR2* (Ex7-128C>T), *CTLA4* (Ex1-61A>G), *IL4* (-588C>T and Ex1-168C>T)] were not consistent with Hardy-Weinberg equilibrium (HWE) among non-Hispanic Caucasian controls using a chi-square test ($P < 0.05$, Table

1). It is notable that the statistical analysis of deviation for the *P* values for these SNPs fell between 0.05 and 0.01. Quality control data were re-checked and the accuracy of each assay not in HWE among controls was confirmed. Evaluation of all SNPs analyzed to date in the study showed that approximately 5% were not consistent with HWE, as expected.

Statistical analysis. Unconditional logistic regression was used to estimate the odds ratios (ORs) and 95% confidence intervals (CIs), adjusting for age (<50, 50-70, >70), race (Caucasian, African-American, other). Analyses adjusted for family history resulted in similar estimates. Analyses limited to non-Hispanic Caucasians (representing 93.2 and 91.6% of all cases and controls, respectively) are shown in Supplementary Tables 1 and 2 and were comparable to analyses that included all study subjects (Tables 3 and 4). In this report, we provide results of individual SNP analyses from models that include all study subjects adjusting for age and sex.

The most prevalent homozygous genotype was used as the reference group. Tests for trend were conducted by assigning the ordinal values 1, 2, and 3 to the most prevalent genotypes in rank order of wild type, heterozygous, and variant homozygous genotypes, respectively. Risks for NHL subtypes were carried out using all controls as the comparison group, to maximize statistical power. NHL subtype comparisons were conducted using unconditional logistic regression by treating one subtype as a "case" and the other one as a "control" in the model.

Since we conducted multiple tests within this data set and there was a chance that some of our results could be false positive findings, we used the Benjamini-Hochberg

method to control for the False Discovery Rate (FDR).[34] The FDR is defined as the expected ratio of erroneous rejections of the null hypothesis to the total number of rejected hypotheses. We applied the FDR method to the *P*-values of the risk for homozygous carriers of the rare vs. common allele, as this provides the greatest potential contrast in effects across genotypes. All *P* values presented are two-sided and all analyses were carried by the Statistical Analysis Software, version 8.02 (SAS Institute Inc, 1996).

Haplotype analysis. Haplotype analyses were conducted within non-Hispanic Caucasians for all genes in which more than one SNP was genotyped. Haplotype block structure was evaluated with the program, HaploView (http://www.broad.mit.edu/personal/jcbarret/haploview/) using the four gamete rule with a minimum frequency of 0.005 for the fourth gamete. Haplotypes were estimated using the Estimation-Maximization algorithm,[35] and overall differences in haplotype frequencies between non-Hispanic Caucasian cases and controls were assessed using the global score test implemented in HaploStats[36] (R Version 1.2.0) adjusting for age. A logistic regression model was used to estimate the effect of individual haplotypes assuming an additive model by using posterior probabilities of the haplotypes as weights to update the regression coefficients in an iterative manner.[36]

Results

NHL cases were comparable to controls with regard to age and ethnicity. However, cases were more likely to have a positive family history of cancer in a first-

degree relative (Table 2). Analyses adjusted for family history resulted in similar estimates (data not shown). SNPs that were significantly associated with risk of all NHL, B cell, or T cell lymphoma are shown in Table 3. In addition, we present results for all *IL10* promoter SNPs as these are used for subsequent haplotype analyses.

SNPs in each of three Th2-related cytokines, *IL4*, *IL5*, and *IL10*, were significantly associated with an increased risk for NHL overall (Table 3). Significant trends were observed for SNPs in *IL10* (-1082A>G; -3575T>A), *IL4* (-1098T>G), and borderline effects for *IL5* (-745C>T). There was no evidence of gene-gene interactions between *IL10*, *IL4*, and *IL5*, although the power was too low to detect such effects. Subsequent analyses by NHL subtype showed that variants in *IL10* and *IL5* were significantly associated with an increased risk of B cell lymphoma, and variants in *IL4*, *IL4R*, and *IL6* were significantly associated with an altered risk of T cell lymphoma (Table 3). The risk estimates for *IL4* (-1098T>G) and *IL6* (-598G>A) SNPs for T cell vs. B cell lymphoma differed significantly ($P = 0.0029$ and $P = 0.016$ for test of heterozygote/homozygote carriers of the rare allele vs. subjects homozygous for the common allele, respectively).

The FDR method[34] was used to adjust the *P*-values from the 39 tests (i.e., total number of SNPs studied) evaluating the association between each SNP and the risk of NHL and from the 78 tests of association for risk of B and T cell lymphoma. After accounting for multiple comparisons, the *IL10* (-3575T>A) SNP remained significantly associated with all NHL (i.e., original *P* value of 0.00098 was adjusted to 0.034) and B cell lymphoma (i.e., original *P* value of 0.00067 was adjusted to 0.032). In addition, the *IL4* (-1098T>G) SNP remained significantly associated with risk of T cell lymphoma (i.e.,

original *P* value of 0.00054 was adjusted to 0.023). FDR-adjusted *P*-values for all other associations shown in Table 3 were above 0.10.

In an exploratory analysis, we further examined the risk of the major B cell histologic subtypes for SNPs that showed significant effects for all B cell lymphoma. The *IL10* (-3575T>A) SNP was significantly associated with increased risk for diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (Table 4). In contrast, the *IL5* variant was associated with increased risk for DLBCL only.

When possible, we estimated haplotypes and analyzed for risk of NHL. For instance, a haplotype analysis of the four SNPs located in the *IL10* proximal and distal promoter regions was conducted. The *IL10* haplotype (-3575T>A, -1082A>G, -819C>T, and -592C>A) A-G-C-C, containing the minor alleles -3575A and -1082G (both previously associated with disease risk) and the common alleles -819C, and -592C, was associated with an increased risk for NHL, particularly B cell lymphoma (OR = 1.54, 95% CI = 1.21-1.96) (Table 5). Since an alternative haplotype T-G-C-C bearing only the -1082G variant was not associated with increased risk for B cell lymphoma, we interpret the results to suggest that the -3575A variant was important in driving the increased risk observed for B cell lymphoma. Interestingly, the T-A-T-A haplotype, containing the common alleles -3575T and -1082A and the rare variants -819T and -592A in the proximal promoter was also associated with increased risk for B cell lymphoma (OR = 1.37, 95% CI = 1.05-1.79). Single analyses of the SNPs, *IL10* -819T and -592A, did not demonstrate an association (Supplementary Table 1), which suggests that another unobserved variant lying on the same haplotype structure or in linkage disequilibrium with the T-A-T-A haplotype could be driving the observed association between the T-A-

T-A haplotype and NHL risk. The inclusion of SNPs outside the promoter region did not yield additional insight into the association between *IL10* and NHL risk (data not shown). Similarly, in a haplotype analysis of the five SNPs studied in *IL4*, we observed a comparable risk to that observed for *IL4* (-1098T>G) SNP (Table 3).

Although additional SNPs were significantly associated with one or more NHL subtypes (i.e., *IL7R* Ex4+33G>A and *JAK3* Ex23+291A>G and T cell lymphoma; *IFNGR1* IVS6-4A>G and follicular lymphoma; Supplementary Tables 3 and 4), the number of subjects with the homozygous genotype was relatively small. Further, none of these SNPs was associated with risk for these subtypes at $P < 0.05$ after correction for multiple comparisons.

Discussion

We report one of the first analyses of the association between SNPs chosen from key immunologic cytokine genes and NHL. This study represents a pathway-based approach towards investigating common genetic variants in the Th1/Th2 cytokine network in a population-based case-control study of non-Hodgkin lymphoma in women in Connecticut. In total, we analyzed 17 SNPs drawn from eleven Th1 genes, 21 SNPs from eight Th2 genes, and 1 SNP from one Th1/Th2 gene. Overall, we observed that common genetic variants in Th2 cytokine genes were associated with risk for NHL. SNPs in the Th2 genes *IL4*, *IL5*, and *IL10* were significantly associated with increased risk of NHL overall. However, there was evidence that the effects were specific to lymphoma subtypes. In particular, SNPs in *IL10* and *IL5* were associated with B cell lymphoma,

whereas SNPs in *IL4*, *IL4R*, and *IL6* were associated with T cell lymphoma. A specific haplotype spanning the promoter region of *IL10* was associated with an increased risk for B cell lymphoma, an effect not apparent in single SNP analyses. This observation suggests that the 'causal' SNP(s) probably are in linkage disequilibrium with SNPs chosen for this study. Follow-up analysis will need to analyze additional SNPs across the ancestral haplotypes of the *IL10* and *IL4* genes.

A pooled analysis of the international InterLymph Consortium of case-control studies of NHL, which included a subset of data on Caucasians from the current study (Table 1), presented results for DLBCL and follicular lymphoma and determined that two promoter SNPs in *IL10,* namely, the *IL10* -3575T>A and -1082A>G SNPs, were associated with risk of NHL, particularly DLBCL.[33] Even when the robust results from our study were excluded from the pooled analysis, the effect remained significant for DLBCL. Here, we have extended the InterLymph analysis of *IL10* variants by evaluating two additional promoter SNPs, -819C>T and –592C>A, and report for the first time that a haplotype containing both variant alleles was associated with B cell lymphoma, and both for DLBCL and follicular lymphoma (Table 5). The results from our study and others[17,33] provide compelling evidence that genetic variation in the *IL10* promoter region plays an important role in the etiology of NHL and deserves further investigation. There is substantial evidence in support of a role for IL-10 in lymphomagenesis. It is a critical mediator of the Th1/Th2 balance, apoptosis potential and regulation of inflammation.[6] A *IL10* knock-out mouse model showed that IL-10 is critical for B-cell lymphomagenesis.[16] IL-10 serum levels have been shown to be prognostic factors for NHL, particularly the DLBCL subtype.[17,37] Elevated levels of IL-10 in the vitreous have been correlated with

primary intraocular lymphoma.[38] *In vitro* laboratory work has explored the functional consequences of *IL10* variants, such as the *IL10* -3575A allele, which appears to be associated with decreased levels of IL-10.[18] Lower IL-10 levels could result in higher TNFα expression, shifting the balance towards Th1 humoral immunity.[39] Indeed, we also found an increased risk for the *TNF*-308A allele for DLBCL (Supplementary Table 4) that was consistent with the pooled risk estimate in the InterLymph study.[33] However, the association was not significant, probably because of limited power.

Previous work has shown that proximal promoter *IL10* haplotypes alter IL-10 secretion as well as expression of the gene.[26,27] In our haplotype analysis, we determined that SNPs either in the promoter or in LD with those tested in our study, were associated with risk for NHL. It is notable that the same *IL10* promoter haplotypes have been associated with a number of immune mediated-diseases, including progression of HIV infection and autoimmune diseases such as lupus erythematosus, graft-versus-host disease following marrow transplantation, and asthma, providing supportive evidence that common genetic variation in the *IL10* genes could influence disease susceptibility further.[40-44]

The other noteworthy finding in our study was that variation in the *IL4* gene is associated with risk of all NHL, particularly T cell lymphoma. Though the number of T cell lymphoma cases in our study was small, the effect was striking and merits follow-up in one of the large international consortia. These results are intriguing because *IL4* plays a key role in the proliferation of T cells.[2,7,45-47] The *IL4* promoter SNPs and haplotypes have been associated with Juvenile Idiopathic Arthritis, severity of infection with respiratory syncytial virus in young children, asthma, fungal infection with *Candida*

albicans in leukemia patients, atopy and inflammatory bowel disease.[48-53] Further, this same *IL4* promoter haplotype has been shown to alter gene expression *in vivo* and *in vitro*.[25,54] The observation that a SNP in the *IL4R* gene was associated with increased risk of T cell lymphoma also underscores the importance of regulating the Th1/Th2 balance. Previous work reported that genetic variants in *IL4R* can affect signal transduction and the level of gene expression of *IL4R*.[21,55]

In summary, we report that common genetic variants in two key genes of the Th2 pathway, namely, *IL10* and *IL4*, could be associated with the risk of NHL and possibly one or more of the major subtypes. It is notable Th2 cytokines have pleiotropic functions including modulating the inflammatory process, response to viral infection and other agents as well as function as autocrine growth factors.[56-58] Our results raise the possibility that a shift in the balance of the Th1/Th2 response caused by genetic variants in key cytokine genes could have important consequences for the pathogenesis of NHL. More extensive genomic analysis of the genes evaluated here, as well as additional genes in the Th2 pathway, is warranted. Further, these findings, although intriguing, require replication in larger studies and ultimately in pooled analyses.

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Table 1. Genes and single nucleotide polymorphisms (SNP) evaluated

Gene	Name	Chromosome Location	SNP database ID
Th1 genes			
IFNG	Interferon, gamma	21q14	rs1861494†, rs2069705†
IFNGR1	Interferon, gamma, receptor 1	6q23-q24	rs3799488†
IFNGR2	Interferon, gamma, receptor 2	21q22,10q22.2	rs2070385, rs1059293*†
IL2	Interleukin 2	4q26-q27	rs2069762§
IL7R	Interleukin 7 receptor	5p13	rs1494555†
IL12A	Interleukin 12, alpha	3p12-q13.2	rs568408, rs582054
IL12B	Interleukin 12B	5q31.1-q33.1	rs3212227
IL15	Interleukin 15	4q31	rs10833 †
IL15RA	Interleukin 15 receptor, alpha	10p15.1	rs2296135†
LTA	Lymphotoxin-alpha	6p21.3	rs909253§, rs2239704
TNF	Tumor necrosis factor	6p21.3	rs1800629§, rs361525, rs1799724
Th2 genes			
IL4	Interleukin 4	5q31.1	rs2243250*, rs2243248, rs2070874*, rs2243290†, rs2243268†
IL4R	Interleukin 4 receptor	16p11.2-p12.1	rs2107356
IL5	Interleukin 5	5q31.1	rs2069812
IL6	Interleukin 6	7p21-24	rs1800795§, rs1800797§
IL10	Interleukin 10	1q31-q32	rs1800871, rs1800872§, rs1800896§, rs3024509†, rs3024496†, rs3024491†, rs1800890§
IL10RA	Interleukin 10 receptor, alpha	11q23	rs9610
IL13	Interleukin 13	5q31	rs20541, rs1800925, rs1295686†
JAK3	Janus kinase 3	19p13.1	rs3008†
Th1/Th2			
CTLA4	Cytotoxic T lymphocyte-associated 4	2q33	rs231775*†

†Genotyped in blood-based samples only.
*HWE $p<0.05$ in non-Hispanic Caucasian controls.
§ Included in the pooling effort by the InterLymph case-control consortium[33] for all non-Hodgkin lymphoma, diffuse large B-cell lymphoma, and follicular lymphoma among Caucasian study subjects.

Table 2. Characteristics of study participants (n=1,115)

Characteristics		Cases (n=518) n (%)	Controls (n=597) n (%)	*P*-Value
Age (years)	<40	43 (8.30%)	51 (8.54%)	0.60
	40-49	59 (11.39%)	66 (11.06%)	
	50-59	109 (21.04%)	109 (18.26%)	
	60-69	132 (25.48%)	144 (24.12%)	
	70+	175 (33.78%)	227 (38.02%)	
Race	Caucasian	497 (95.95%)	561 (93.97%)	0.14
	Non-Hispanic	483 (93.24%)	547 (91.62%)	
	Hispanic	12 (2.32%)	14 (2.34%)	
	Unknown	2 (0.39)	0 (0%)	
	African-American	16 (3.09%)	17 (2.85%)	
	Other	5 (0.97%)	19 (3.18%)	
Family history*	No	110 (21.24%)	147 (24.62%)	0.06†
	NHL‡	9 (1.74%)	3 (0.50%)	
	Other cancer	399 (77.03%)	447 (74.87%)	
DNA source	Blood	461 (89.00%)	535 (89.61%)	0.74
	Buccal cells	57 (11.00%)	62 (10.39%)	
Case pathology§	All B cell	411 (79.34%)	-	
	Diffuse large B-	161 (31.08%)	-	
	Follicular	119 (22.97%)	-	
	SLL/CLL	59 (11.39%)	-	
	Marginal Zone	35 (6.76%)	-	
	Other	37 (7.14%)	-	
	All T cell	39 (7.53%)	-	
	NOS	68 (13.13%)	-	

* Family history of cancer in first degree relatives.

† Exact test.

‡ Non-Hodgkin Lymphoma.

§ DLBL=Diffuse large B-cell lymphoma; CLL/SLL= B-cell chronic lymphocytic leukemia/prolymphocytic leukemia/small lymphocytic lymphoma; MZBL=Marginal zone B-cell lymphoma

Table 3. Association between Th1/Th2 cytokine polymorphisms and non-Hodgkin lymphoma (NHL)*

Gene name SNP database ID (nucleotide change)	All NHL				B-cell lymphoma			T-cell lymphoma		
	Controls n (%)	Cases n (%)	Odds ratio (95% CI)	*P*-Value	Cases n (%)	Odds ratio (95% CI)	*P*-Value	Cases n (%)	Odds ratio (95% CI)	*P*-Value
IL4 rs2243248 (-1098T>G)										
TT	508(88)	411 (83)			334 (85)			22 (65)		
GT or GG	70(12)	82 (17)	1.49 (1.05-2.11)	**0.026**	59 (15)	1.33 (0.91-1.95)	0.14	12 (35)	3.84 (1.79-8.22)	**<0.001**
NA†	3	6			3			3		
ND‡	3	1			1			0		
IL4R rs2107356 (-28120C>T)										
CC	200(36)	150 (32)			124 (34)			7 (20)		
CT	258(47)	249 (54)	1.30 (0.98-1.71)	0.069	190 (51)	1.17 (0.87-1.58)	0.30	22 (63)	2.71 (1.09-6.75)	**0.032**
TT	95(17)	65 (14)	0.89 (0.61-1.31)	0.56	55 (15)	0.89 (0.60-1.34)	0.59	6 (17)	2.06 (0.65-6.56)	0.22
CT or TT	353(64)	314 (68)	1.19 (0.91-1.55)	0.21	245 (66)	1.10 (0.83-1.45)	0.52	28 (80)	2.55 (1.04-6.21)	**0.04**
Trend				0.96			0.87			0.14
NA	14	16			13			1		
ND	6	7			7			0		
IL5 rs2069812 (-745C>T)										
CC	273(49)	219 (46)			172 (45)			18 (51)		
CT	238(42)	199 (41)	1.05 (0.81-1.37)	0.70	160 (42)	1.08 (0.82-1.43)	0.58	13 (37)	0.83 (0.4-1.73)	0.62
TT	51(9)	62 (13)	1.63 (1.04-2.54)	**0.032**	50 (13)	1.76 (1.11-2.81)	**0.017**	4 (11) §		
CT or TT	289(51)	261 (54)	1.14 (0.89-1.46)	0.31	210 (55)	1.18 (0.91-1.54)	0.22	17 (49)	0.81 (0.4-1.65)	0.56
Trend				0.08			**0.046**			
NA	10	5			4			1		
ND	1	4			4			0		
IL6 rs1800795 (-174 G>C)										
GG	241(41)	211 (41)			160 (39)			23(61)		
CG	264(45)	231 (45)	0.97 (0.75-1.26)	0.83	182 (45)	0.99 (0.75-1.31)	0.95	14(37)	0.56 (0.28-1.13)	0.11
CC	85(14)	68 (13)	0.90 (0.62-1.31)	0.58	64 (16)	1.09 (0.74-1.61)	0.65	1 (3)		
CG or CC	349(59)	299 (59)	0.96 (0.75-1.22)	0.71	246 (61)	1.02 (0.78-1.32)	0.91	15(39)	0.46 (0.23-0.92)	**0.027**

Trend				0.60			0.73			
NA	3	4			3			1		
ND	4	4			2			0		
IL6 rs1800797 (-598G>A)										
GG	233(41)	212 (43)			159 (41)			24 (65)		
AG	254(44)	217 (44)	0.92 (0.71-1.20)	0.54	171 (44)	0.95 (0.71-1.26)	0.70	12 (32)	0.47 (0.23-0.97)	**0.041**
AA	84(15)	64 (13)	0.82 (0.56-1.19)	0.30	61 (16)	1.01 (0.69-1.50)	0.95	1 (3)		
AG or AA	338(59)	281 (57)	0.89 (0.70-1.15)	0.38	232 (59)	0.96 (0.74-1.26)	0.78	13 (35)	0.38 (0.19-0.78)	**0.008**
Trend				0.29			0.94			
NA	18	14			10			2		
ND	8	9			9			0		
IL10 rs1800871 (-819C>T)										
CC	329 (57)	274 (56)			212 (54)			24 (67)		
CT	211 (37)	191 (39)	1.10 (0.85-1.42)	0.46	162 (41)	1.22 (0.93-1.60)	0.15	9 (25)	0.56 (0.25-1.25)	0.16
TT	34 (6)	26 (5)	0.97 (0.56-1.67)	0.92	17 (4)	0.84 (0.46-1.56)	0.59	3 (8)		
CT or TT	245 (43)	217 (44)	1.08 (0.85-1.39)	0.52	179 (46)	1.17 (0.90-1.52)	0.24	12 (33)	0.64 (0.31-1.32)	0.22
Trend				0.66			0.50			
NA	4	4			3			1		
ND	3	3			2			0		
IL10 rs1800872 (-592C>A)										
CC	331 (59)	273 (57)			213 (55)			24 (65)		
AC	189 (34)	174 (36)	1.14 (0.88-1.48)	0.33	146 (38)	1.24 (0.94-1.64)	0.13	9 (24)	0.62 (0.28-1.38)	0.24
AA	43 (8)	35 (7)	1.04 (0.65-1.69)	0.86	25 (7)	0.97 (0.57-1.65)	0.92	4 (11)		
AC or AA	232 (41)	209 (43)	1.12 (0.88-1.44)	0.36	171 (45)	1.19 (0.92-1.56)	0.19	13 (35)	0.73 (0.36-1.48)	0.38
Trend				0.48			0.39			
NA	5	1			1			0		
ND	13	13			10			0		
IL10 rs1800896 (-1082A>G)										
AA	184 (31)	137 (27)			103 (25)			11 (29)		
AG	305 (52)	260 (51)	1.14 (0.86-1.51)	0.35	209 (51)	1.23 (0.91-1.66)	0.18	20 (53)	1.07 (0.50-2.29)	0.86

GG	98 (17)	113 (22)	1.53 (1.08-2.17)	**0.018**	94 (23)	1.68 (1.15-2.44)	**0.0067**	7 (18)	1.22 (0.46-3.27)	0.69
AG or GG	403 (69)	373 (73)	1.24 (0.95-1.61)	0.12	303 (75)	1.34 (1.01-1.78)	**0.045**	27 (71)	1.11 (0.54-2.28)	0.79
Trend				**0.022**			**0.0074**			0.70
NA	2	1			0			1		
ND	8	7			5			0		
IL10 rs1800890 (-3575T>A)										
TT	261 (44)	188 (37)			145 (36)			17 (45)		
AT	280 (47)	244 (48)	1.21 (0.94-1.56)	0.15	197 (49)	1.27 (0.96-1.67)	0.09	16 (42)	0.90 (0.44-1.82)	0.76
AA	56 (9)	78 (15)	1.94 (1.31-2.87)	**<0.001**	64 (16)	2.05 (1.36-3.11)	**<0.001**	5 (13)	1.44 (0.50-4.10)	0.50
AT or AA	336 (56)	322 (63)	1.33 (1.04-1.70)	**0.022**	261 (64)	1.40 (1.08-1.82)	**0.012**	21 (55)	0.98 (0.51-1.92)	0.96
Trend				**0.0016**			**<0.001**			0.73
NA	0	3			2			1		
ND	0	3			2			0		

* Adjusted for age and race. Further adjustment of family history yielded similar results.
† NA: No amplification observed.
‡ ND: Amplification occurred but genotype could not be determined.
§ Odds ratio not given for cells with less than 5 subjects.

Table 4. Association between TH1/TH2 cytokine polymorphisms and common B-cell subtypes of non-Hodgkin lymphoma*

Gene name		Diffuse large B-cell lymphoma			Follicular		
SNP database ID (nucleotide change)	**Controls n (%)**	**Cases n (%)**	**Odds ratio (95% CI)**	***P*-Value**	**Cases n (%)**	**Odds ratio (95% CI)**	***P*-Value**
IL5 rs2069812 (-745C>T)							
CC	273(49)	62(41)			45(42)		
CT	238(42)	66(44)	1.26 (0.85-1.86)	0.25	52(49)	1.37 (0.88-2.12)	0.17
TT	51(9)	23(15)	2.28 (1.25-4.15)	**0.007**	9(8)	1.19 (0.51-2.76)	0.69
CT or TT	289(51)	89(59)	1.41 (0.97-2.04)	0.07	61(58)	1.34 (0.87-2.05)	0.18
Trend				**0.012**			0.28
NA†	10	1			2		
ND‡	1	2			2		
IL10 rs1800871 (-819C>T)							
CC	329(57)	81(52)			53(49)		
CT	211(37)	67(43)	1.33 (0.92-1.93)	0.13	51(47)	1.54 (1.00-2.36)	**0.047**
TT	34(6)	7(5)	0.92 (0.39-2.17)	0.85	5(5)	1.07 (0.40-2.91)	0.89
CT or TT	245(43)	74(48)	1.28 (0.89-1.83)	0.18	56(51)	1.48 (0.98-2.25)	0.063
Trend				0.36			0.14
NA	4	2			1		
ND	3	0			1		
IL10 rs1800872 (-592C>A)							
CC	331(59)	82(54)			55(50)		
AC	189(34)	62(41)	1.38 (0.94-2.02)	0.10	44(40)	1.45 (0.93-2.25)	0.10
AA	43(8)	8(5)	0.81 (0.36-1.80)	0.61	10(9)	1.57 (0.74-3.36)	0.24
AC or AA	232(41)	70(46)	1.28 (0.89-1.84)	0.19	54(50)	1.47 (0.97-2.23)	0.071
Trend				0.49			0.08
NA	5	1			0		
ND	13	4			1		
IL10 rs1800896 (-1082A>G)							
AA	184(31)	40(25)			31(26)		
AG	305(52)	80(50)	1.19 (0.78-1.82)	0.42	63(53)	1.26 (0.79-2.02)	0.34
GG	98(17)	40(25)	1.80 (1.09-2.99)	**0.022**	24(20)	1.40 (0.77-2.53)	0.27
AG or GG	403(69)	120(75)	1.34 (0.90-2.00)	0.15	87(74)	1.30 (0.83-2.03)	0.26

Trend				**0.027**			0.24
NA	2	0			0		
ND	8	1			1		
IL10 rs1800890 (-3575T>A)							
TT	261(44)	58(36)			40(34)		
AT	280(47)	76(48)	1.20 (0.82-1.76)	0.35	60(51)	1.44 (0.93-2.23)	0.11
AA	56(9)	26(16)	2.02 (1.17-3.49)	**0.012**	18(15)	2.03 (1.08-3.81)	**0.029**
AT or AA	336(56)	102(64)	1.34 (0.93-1.92)	0.12	78(66)	1.54 (1.01-2.34)	**0.043**
Trend				**0.022**			**0.02**
NA	0	0			0		
ND	0	1			0		

* Adjusted for age and race.

† NA: No amplification observed.

‡ ND: Amplification occurred but genotype could not be determined.

Table 5. Odds ratios and 95% confidence intervals for the association between common *IL10* haplotypes in distal and proximal promoter region and all non-Hodgkin lymphoma (NHL), and B cell, T cell, Diffuse large B-cell lymphoma, and Follicular lymphoma among non-Hispanic Caucasians

Haplotype*	Controls %	%	All NHL Odds ratio† (95% CI)	*P*- Valu	%	B cell Odds ratio† (95% CI)	*P*- Value	%	T cell Odds ratio† (95% CI)	*P*- Valu	%	Diffuse large B-cell lymphoma Odds ratio† (95% CI)	*P*- Value	%	Follicular Odds ratio† (95% CI)	*P*- Valu
T-A-C-C	32.4	27.3	1.0	-	25.8	1.0	-	34.8	1.0	-	24.3	1.0	-	24.1	1.0	-
A-G-C-C	33.0	38.8	1.44 (1.15-1.80)	**0.0017**	39.3	1.54 (1.21-1.96)	**<0.001**	36.8	1.04 (0.56-1.92)	0.90	40.7	1.67 (1.19-2.34)	**0.003**	39.4	1.70 (1.15-2.50)	**0.0074**
T-A-T-A	22.4	23.5	1.28 (1.00-1.64)	0.05	24.0	1.37 (1.05-1.79)	**0.02**	19.6	0.86 (0.43-1.73)	0.68	25.0	1.54 (1.06-2.23)	**0.023**	27.4	1.73 (1.14-2.63)	**0.011**
T-G-C-C	10.4	8.8	1.01 (0.73-1.40)	0.95	9.1	1.10 (0.78-1.57)	0.58	8.8	0.81 (0.32-2.00)	0.64	9.7	1.25 (0.77-2.01)	0.37	6.2	0.83 (0.44-1.56)	0.57
Global test†				**0.029**			**0.01**			0.97			**0.043**			**0.017**

*Order of SNPs comprising the *IL10* haplotypes: -3575T>A, -1082A>G, -819C>T, and -592C>A.

†Odds ratios and global test are adjusted for age.

‡Percentages may not add to 100% because of the presence of rare haplotypes not presented in this table.

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